PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/014556	22.12.2004	23.12.2003

International Patent Classification (IPC) or both national classification and IPC
C07F9/38

Applicant
LYOGEN LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/014556

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 5-8

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 5-8

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-4

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-4
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/EP2004/014556

Re Item III.

The present examination is limited to claims 1-4 due to a restricted search report in view of an objecton with respect to lack of unity of invention (Rule 13.1 PCT).

Re Item IV.

The separate inventions/groups of inventions are:

1-4
Process for the preparation of diphosphonic acids
5-8
Ibandronic acid monosodium salt in the amorphous form and corresponding compositions and process

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

Claim 1 is directed to a process for the preparation of diphosphonic acids employing a carboxylic acid derivative, phosphorus oxychloride and phosphorous acid in a specific molar ratio in the absence of solvents. Claim 5 deals with a monosodium salt of ibandronic acid in the amorphous form. For the purpose of unity of invention it is required to define a single general inventive concept which represents a contribution over the prior art. Thus a special technical feature needs to be present in all subject-matter claimed. In the present case the problem to be solved is the provision of a process (claim 1) giving an improved access to known diphosphonic acids according to general formula (I). Furthermore the problem to be solved according to claim 5 is the provision of Ibandronic acid as a monosodium salt in the amorphous form with possibly improved pharmacological properties. Free Ibandronic acid which can be obtained with a process according to claim 1 is known from documents D5 (Widler et al.) and D7 (EP0252504). In view of the documents of the prior art, possible contributions diverge in different directions and are thus not so linked to form a single inventive concept, which would support the unity of invention.

Re Item V.

Reference is made to the following documents:

D1: US-A-4 407 761 (BLUM ET AL) 4 October 1983
D2: DE 27 02 631 A1 (HENKEL KGAA) 27 July 1978
D3: DE 26 58 961 A1 (JOH.A. BENCKISER GMBH; JOH. A. BENCKISER GMBH, 6700 LUDWIGSHAFEN; JOH.) 29 June 1978
D4: IT-B-1 230 503 (ISTITUTO GENTILI S.P.A) 25 October 1991
D5: WIDLER L ET AL: "HIGHLY POTENT GEMINAL BIPHOSPHONATES. FROM PAMIDRONATE DISODIUM (AREDIA) TO ZOLEDRONIC ACID (ZOMETA)" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, no. 17, 15 August 2002 (2002-08-15), pages 3721-3738,
D6: KIECZYKOWSKI ET AL: "Preparation of (4-Amino-1-Hydroxbutylidene)bisphosphonic Acid Sodium Sal, MK-217 (Alendronate Sodium). An Improved Procedure for the Preparation of 1-Hydroxy-1,1-bisphosphonic Acids" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 60, 1995, pages 8310-8312,
D7: EP-A-0 252 504 (BOEHRINGER MANNHEIM GMBH) 13 January 1988

The present application is directed to a process for the preparation of diphosphonic acids according to general formula (I). The process involves the reaction of a carboxylic acid, phosphorus oxychloride and phosphorous acid in a specific molar ratio in the absence of further solvents.

Documents D5-D7 describe processes for the preparation of diphosphonic acids falling under the scope of general formula (I), which make use of chlorobenzene as a solvent (D5,D7) or in the presence of methanesulfonic acid (D6).
D4 anticipates a process (example 2) in the absence of a solvent, but using PCl_3 instead of $POCl_3$.

The most relevant document of the prior art is represented by D1, which already contains an example using a carboxylic acid, H_3PO_3 and $POCl_3$ in the absence of any solvent. Documents D2 (examples 1,2) and D3 (example 1) contain further examples for such procedures.
However the subject-matter of claim 1 of the present application is specified by a molar ratio of carboxylic acid : phosphorus oxychloride : phosphorous acid of 1 : 2-4 : 8-12. No document of the prior art provides examples which make use of such a high excess of acid. Furthermore D2 and D3 are different in that the examples presented in these documents use beta-alanin as a starting material. Thus the requirements of Art. 33(2) PCT are met.

Document D1 (column 3) specifies that it is not necessary to use a diluent, when a mixture of H_3PO_3 and $POCl_3$ is used as the phosphonating agent. D2 (page 2) and D3 (pages 2-3) also discuss the difficulties that are encountered when a solvent is used. Thus the omission of a diluent cannot represent a nonobvious contribution over the prior art. The specification of a molar ratio according to claim 1 only represents a feature which renders the subject-matter formally novel. The description does not provide any data or comparative examples which show any possible advantages of the chosen molar ratios. E.g. the given yields are comparable to those of the prior art and those examples given in D2 and D3 were even performed on a larger scale thus having a higher resemblance to an industrial scale production.
The involvement of an inventive step cannot be acknowledged (Art. 33(3) PCT).